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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/010,245 | 12/07/2001 | Paul J. Carter | P0927C2 | 8478 |

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| EXAMINER | |
|---|---|
| GUCKER, STEPHEN | |
| ART UNIT | PAPER NUMBER |
| 1649 | |
| MAIL DATE | DELIVERY MODE |
| 10/02/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/010,245 | CARTER ET AL. | |
| | Examiner | Art Unit | |
| | STEPHEN GUCKER | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-23,25,28-39,42-55 and 57-81* is/are pending in the application.

4a) Of the above claim(s) *1-23 and 29-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,28,39,42-55,57-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

***Response to Amendment***

1. In view of the Appeal Brief filed on 11/13/07, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

4. Claims 25, 28, 39, 42-55, and 57-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24-28 and 52-100 of copending Application No. 11/533,709. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims are a

sub-genus of the generic instant claims because the copending claims are limited to the sub-genus of $C_H3$ antibody constant domains and specifically numbered amino acid residues, while the instant claims are generic for any polypeptide domains and recite no specifically numbered amino acid residues in the $C_H3$ antibody constant domain. Therefore, the copending claims are a sub-genus of the instant genus claims because the copending claims encompass a sub-genus that is smaller than the instant genus claims, but said sub-genus is completely encompassed by the claimed instant genus. Accordingly, a species-genus relationship exists between the copending claims and the instant claims, and the copending claims render the instant claims obvious because the copending claims anticipate the instant claims and the copending species or sub-genus renders the instant genus claims obvious. See, e.g., *In re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 25, 28, 39, 42-55, and 57-81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to a genus of heteromultimers comprising a first polypeptide and a second polypeptide that meet at an engineered interface wherein said engineered interface comprises a first polypeptide with a protuberance that is positionable in a cavity of the second polypeptide, or a first polypeptide with a cavity that is

positionable in a protuberance of a second polypeptide, or both, wherein the engineered protuberance or cavity have been introduced into the interface such that a greater ratio of heteromultimer:homomultimer form than for a multimer having a non-engineered interface (see instant claims 1 and 39). The specification evidences actual reduction to practice to 8 species (see Table 4, page 61), however, all 8 species are descriptive concerning only the $C_H3$ antibody constant domain, and not to the broad genus of polypeptides in general. Further limiting, the 8 species are not descriptive concerning the entire $C_H3$ antibody constant domain region, but only to 2 specific pairings of a total of 4 numbered amino acid residues. Specifically, amino acid residue T366 can be engineered at the interface with amino acid residue Y407 (or vice versa) of the $C_H3$ antibody constant domain, and amino acid residue F405 can be engineered at the interface with amino acid residue T394 (or vice versa) as shown in Table 4, page 61. In addition, both pairings can be in the same heteromultimer (bottom 3 lines of most preferred mutants in Table 4). However, both the specification (pages 35-36) and the art indicate that in order to produce heteromultimers that meet the limitations of the claims, the three-dimensional structure of the heteromultimer must be known down to the resolution of individual atoms by such techniques as X-ray crystallography, and determining the geometrical fitting of two (or more) polypeptide molecules in a protein-protein interaction is exceedingly complex and requires the knowledge of using pairs of critical points in combination with an adequate description of the respective molecular surfaces of the two polypeptides (Norel et al., page 933; see also Figure 1). The crystallographic structure of the genus of the vast majority of isolated heteromultimers is not known. Such knowledge is necessary in order to adequately describe which amino acid residues of a first polypeptide are in the appropriate

three-dimensional geometric position (and distance) in relation to amino acid residues in a second polypeptide so that a polypeptide to polypeptide interface can be engineered with the appropriate protuberances and cavities as required by the claims. However, neither the specification nor the general knowledge of those skilled in the art provide evidence of any engineered interface of a generic polypeptide heteromultimer which would be expected to be common to the members of the genus as a whole because there is no such thing as a "generic" polypeptide heteromultimer as they come in an almost infinitely complex variety of different amino acid residues, chain lengths, and especially and most pertinent to this discussion, geometric configurations (see Norel et al., Table III). In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by members of the genus, because the pairing of only 4 specifically numbered amino acid positions in the $C_H3$ antibody constant domain region is not representative of the claimed genus. Consequently, since applicant was in possession only of the pairings at the engineered interface of only 4 specifically numbered amino acid positions in the $C_H3$ antibody constant domain region and since the art recognized that an adequate description of the respective molecular surfaces of two polypeptides is required (Norel et al., page 933), the disclosure does not provide an adequate description of the broad genus of polypeptide heteromultimer engineered interfaces or $C_H3$ antibody constant domain region engineered interfaces that meet the structural (protuberances and cavities) and functional (heterodimer over homodimer formation) limitations of the claimed genus. Therefore, the applicant was not in possession of the genus of polypeptide heteromultimers with engineered interfaces as encompassed by the instant claims.

6. Claims 25, 28, 39, 42-55, and 57-81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The "greater ratio of heteromultimer:homomultimer forms than for a multimer..." is vague and confusing since the terms homomultimer and multimer have no antecedent basis in the claims and the term "heteromultimer:homomultimer" is indefinite and not disclosed in the specification. Furthermore, it is not clear which "homomultimer" is being referred to (first or second polypeptide?) when the specification discloses that "heteromultimer" is a molecule comprising at least a first polypeptide and a second polypeptide, wherein the second polypeptide differs in amino acid sequence from the first polypeptide..." (page 12, lines 22-24).

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 25, 28, 42-43, 45-47, 51, 53-54, 66, and 68 are rejected under 35 U.S.C. 102(a) as being anticipated by Zhang et al. ("Zhang"; June 1994). Zhang discloses mutated retinoid X receptors (RXR) that have various amino acid mutations as recited in the instant claims that favor heterodimer formation over homodimer (Figures 3, 4, and 5).

9. Claims 25, 28, 39, 42-43, 45-47, 51-55, 66-69, 71-73, 75-78, and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Tso et al. (WO 93/11162; "Tso") in light of Goodman et al. ("Goodman") and Landschulz et al. (IDS filed 12/7/01, reference 19; "Landschulz"). Tso

et al. teach a bispecific antibody heteromultimer comprising a first and second polypeptide which meet at an interface, wherein the interface of the first polypeptide comprises a protuberance created by a helix of a leucine zipper motif, which is positionable into a cavity created by a complementary leucine zipper helical interface of the second polypeptide (abstract, pages 2-7, and Figures 1 and 2). Goodman describes this leucine zipper interface as packing "knobs" into "holes" (abstract), which is also the terminology used by the instant inventors (see IDS filed 12/7/01, reference 28, Ridgway et al.) to describe the instant invention. Landschulz describes the leucine zipper interface as "interdigitating protrusions" (Figure 5). (Note: Goodman and Landschulz are only used here to illustrate an inherent feature of the engineered leucine zipper, and not in combination with Tso to create an obviousness rejection). To create this set of protuberance-and-cavity-containing polypeptides, plasmid comprising native genomic nucleic acid sequence encoding mouse IgG2a was altered via PCR to comprise the $C_H1$ and hinge constant domains from IgG2a fused to nucleic acid replacing $C_H3$ sequence and encoding the Fos or Jun leucine zipper domains. The Fos and Jun zippers are different polypeptides and have a much greater tendency to form heterodimers than homodimers (page 9). Various binding domains and compositions are disclosed on pages 17-18, immunoadhesins on page 19. The leucine zipper sequences used by Tso are disclosed in Figure 1 and comprise the recited amino acids of the instant claims.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is 571-272-0883. The examiner can normally be reached on Mondays through Fridays from 0930 to 1800.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/S. G./

Examiner, Art Unit 1649

Stephen Gucker

October 2, 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649